PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P200302009WO	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/DK2004/000841	International filing date *(day/month/year)* 02.12.2004	Priority date *(day/month/year)* 02.12.2003
International Patent Classification (IPC) or national classification and IPC INV. A61K31/465 A61K47/48 A61K47/10		
Applicant FERTIN PHARMA A/S		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.09.2005	06.04.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vermeulen, S Telephone No. +49 89 2399-7520

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000841

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-9 as originally filed

   Claims, Numbers

   1-22 filed with the demand

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/DK2004/000841

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-21
	No:	Claims	1,2,22
Inventive step (IS)	Yes:	Claims	3-21
	No:	Claims	1,2,22
Industrial applicability (IA)	Yes:	Claims	1-22
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (SEPARATE SHEET)

International application No.
PCT/DK2004/000841

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following document/s/:
   D1: US-A-3 901 248 (LICHTNECKERT S. ET AL) 26 August 1975
   D2: WO 94/08572 A (ALZA CORP) 28 April 1994
   D3: US-B1-6 586 449 (WALLING JOHN ALLEN) 1 July 2003

2. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1, 2 and 22 is not new in the sense of Article 33(2) PCT. The documents D1, D2 and D3 disclose compositions which fall within the definition of the above mentioned claims, since they disclose products comprising a mixture of (i) a nicotine/resin complex and (ii) a polyol. It should be noted that the term "*intimate mixture*" has no well-recognised meaning and should thus be considered in its broadest possible meaning, i.e. any product in which components (i) and (ii) are mixed together. The same applies to the term "*reaction product*", which encompasses in its broadest sense any possible form of interaction between (i) and (ii). Hence, any product comprising a mixture of components (i) and (ii) is also considered to comprise a "*reaction product*" of (i) and (ii).

2.1 D1 discloses chewable compositions comprising a nicotine/ion exchange resin complex and an organic polyol such as sucrose (eg. examples 1-6, 8 and 10) or sorbitol (e.g. examples 7 and 9). Nicotine/resin complex is mixed together with the polyol and further additives into a molten gum base.

2.2 D2 (cf. example 3) discloses a drug reservoir composition comprising a mixture of 60% nicotine/resin complex and 20% micronized sorbitol. The resin content in the complex is 51%, corresponding to a resin/polyol ratio of 1,53:1.

2.3 D3 discloses a nicotine composition comprising a mixture of cation exchange resin, polyol and nicotine, having a resin/polyol ratio of 1:1 to 5:1 (cf. column 2, lines 59-63 ; examples 1-6). Although D3 does not disclose the incorporation of said mixture in a chewing gum, this is considered an obvious alternative to the skilled person,

especially in view of the teaching of D1 (Article 33(3) PCT).

3. The method of preparation according to claims 3-20 and the product obtainable by said method as defined in claim 21 are considered novel and inventive over the state of the art (Art. 33(2)(3) PCT).

3.1 The document D3 is regarded as being the closest prior art to the subject-matter of claim 3-21, since it shows a similar method comprising the preparation of an aqueous nicotine/resin/polyol slurry followed by removing water from said slurry.

3.2 The subject-matter of claims 3-21 differs from the method known in D3 in that the complexation of nicotine and the cation exchange resin is done before addition of the polyol to said complex. In D3, however, the cation exchange resin is first mixed with the polyol in order to achieve complexation and subsequently the resin/polyol complex is contacted with nicotine. The obtained product is considered different.

3.3 The method according to the present claims provides a nicotine composition with improved release rate (at least 80% over a 10 minute period) as compared to D3 (70-77% over a 10 minute period). None of the prior art documents suggested to modify the method disclosed in D3 in order to obtain the presently claimed method and product obtainable by said method providing a higher nicotine release rate.

4. The compositions and methods of preparation defined in claims 1-22 are considered to be industrially applicable and accordingly meet the requirements of Art.33(4) PCT.

CLAIMS (amended 13 September 2005)

1. A nicotine delivery product comprising an intimate mixture of the reaction product of a nicotine/cation exchange resin complex forming reaction and an organic polyol.

2. A nicotine delivery product according to claim 1, characterized in that the ratio of resin to polyol is from about 1:1 to about 10:1, preferably from 2:1 to 8:1 and most preferably about 2.4:1

3. A method of preparing a nicotine delivery product, said method comprising (a) mixing an aqueous suspension of a nicotine/cation exchange resin complex with an organic polyol or an aqueous solution thereof, and (b) removing water from the mixture to produce said nicotine delivery product.

4. A method of preparing a nicotine delivery product, said method comprising

(a) mixing an aqueous solution of nicotine with a cation exchange resin thereby forming a nicotine/cation exchange resin complex,

(b) admixing with said complex of step (a) in aqueous suspension an organic polyol or an aqueous solution thereof to form an aqueous slurry of nicotine/cation exchange resin complex incorporating polyol, and

(c) removing water from said slurry to produce said nicotine delivery product.

5. A method according to claim 3 or 4 wherein the cation exchange resin is selected from the group consisting of

(i) a methacrylic, weakly acidic type of resin containing carboxylic functional groups

(ii) a polystyrene, strongly acidic type of resin containing sulfonic functional groups, and

(iii) a polystyrene, intermediate acidic type of resin containing phosphonic functional groups.

6. The method according to claim 5 wherein the cation exchange resin is a methacrylic, weakly acidic type of resin containing carboxylic functional groups.

7. The method according to claim 6 wherein the cation exchange resin is polacrilex (Amberlite® IRP64).

8. A method according to any one of claims 3-7 wherein the organic polyol is a non-toxic C_2 to C_{12} linear or branched hydrocarbon having at least 2 hydroxy groups.

9. A method according to claim 8 wherein the organic polyol is selected from the group consisting of 1,2-propanediol, 1,3-propanediol, 1,6-hexanediol, glycerol and sorbitol.

10. A method according to any one of claims 3-7 wherein the organic polyol is a non-toxic C_5 to C_{12} cyclic or heterocyclic hydrocarbon having at least 2 hydroxy groups.

11. A method according to claim 10 wherein the organic polyol is selected from the group consisting of hexahydroxy cyclohexane (inositol) and mono- and disaccharides.

12. A method according to claim 11 wherein the organic polyol is glucose, fructose or sucrose.

13. The method according to any one of claims 3-12, wherein the concentration of nicotine in said aqueous solution of nicotine is from about 5% by weight to about 50% by weight.

14. The method according to any one of claims 3-13, wherein the ratio of cation exchange resin to nicotine is from 1:1 to 10:1.

15. The method according to claim 14, wherein the ratio of cation exchange resin to nicotine is from 2:1 to 6:1.

16. The method according to claim 14, wherein the ratio of cation exchange resin to nicotine is about 4:1.

17. The method according to any one of claims 3-16, wherein the ratio of cation exchange resin to organic polyol is from 1:1 to 10:1.

18. The method according to claim 17, wherein the ratio of cation exchange resin to organic polyol is from 2:1 to 8:1.

19. The method according to claim 17, wherein the ratio of cation exchange resin to organic polyol is about 2.4:1.

20. A method of preparing a nicotine delivery product having a nicotine release rate of at least 80 % over a 10 minute period, said method comprising

(a) mixing an aqueous solution of nicotine with a cation exchange resin selected from the group consisting of

(i) a methacrylic, weakly acidic type of resin containing carboxylic functional groups,

(ii) a polystyrene, strongly acidic type of resin containing sulfonic functional groups, and

(iii) a polystyrene, intermediate acidic type of resin containing phosphonic functional groups

thereby forming a nicotine/cation exchange resin complex,

(b) admixing with said complex of step (a) an organic polyol or an aqueous solution thereof to form an aqueous slurry of nicotine/cation exchange resin complex incorporating polyol, and

(c) removing water from said slurry to produce said nicotine delivery product.

21. A nicotine delivery product obtainable by a method according to any one of claims 3-20.

22. A chewable gum composition comprising a chewing gum base and a nicotine delivery product as defined in claims 1-3 or prepared by the method defined in any one of claims 3-21 substantially uniformly distributed in said chewing gum base.